REMARKS

Introductory Comments

Claims 3-5, 8, 45 and 46 were examined in the Office Action under reply and stand rejected under (1) 35 U.S.C. §103(a); and (2) the judicially created doctrine of obviousness type double patenting. These rejections are respectfully traversed for reasons discussed below.

Applicants note with appreciation the withdrawal of the previous rejections under 35 U.S.C. §102 and under the judicially created doctrine of double patenting over USSN 10/612,884.

Overview of the Foregoing Amendments

Claims 3-5, 8, and 33 have been canceled. Claim 42 has been amended to depend from a non-canceled claim. Claims 45 and 46 have been amended to recite that each of the HCV polypeptides is provided individually. Support for this amendment can be found throughout the specification at, e.g., page 24, lines 10-12.

The foregoing amendments are made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

Applicants request rejoinder of the withdrawn method claims upon an indication that the composition claims are allowable.

35 U.S.C. §103

Claims 5 and 8 remain rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the reference of Cho et al., *Vaccine* (1999) 17:1136-1144 ("Cho") in view of Lagging et al., *J. Virol.* (1995) 69:5859-5863 ("Lagging") or Geissler et al., *J. Immunol.* (1997) 159:5107-5113; ("Geissler"). Applicants assert for reasons of record that claims 5 and 8 are not obvious over the stated combination. Nevertheless, solely for purposes of advancing prosecution, claims 5 and 8 have been canceled. Withdrawal of this basis for rejection is therefore respectfully requested.

Claims 3-5, 8, 45 and 46 were rejected under 35 U.S.C. §103(a) as being unpatentable over PCT Publication No. WO 97/38474 to Liao et al. ("Liao"), Beld et al., *Hepatology* (1999) 29:1288-1298 ("Beld") and PCT Publication No. WO 97/44469 to Valenzuela et al. ("Valenzuela"). Liao is said to describe a composition comprising an HCV core polypeptide in combination with HCV NS5 and NS3/4. Beld is cited for teaching that HCV is an RNA virus with many genotypes "wherein the variations or mutation unexpectedly occur in many locations spreading in core, NS3, NS4 and NS5 regions." Office Action, page 7. Valenzuela purportedly teaches a method of using a fusion polypeptide that expresses multiple epitopes of different structural and non-structural proteins from different genotypes of HCV strains. The Office Action alleges:

> Therefore, obviously to make such an immunogenic composition capable of induce a significant immune response against more than one genotypes of HCV, one of ordinary skill in the art at the time the invention was filed would have been motivated by the cited references to construct an antigenic fusion protein comprising as much as possible antigen epitopes of HCV core, NS345ab that must have been derived from different genotypes or strains of HCV, and preferably in the presence of an adjuvant.

Office Action, page 7. Applicants respectfully traverse the rejection and the supporting remarks.

In particular, Liao describes the use of an unprocessed core region fused with an adjacent region from the polyprotein (i.e., a core-envelope protein) in combination with an NS5 protein, or in combination with an unprocessed NS3-NS4 fusion. These combinations are used in various detection assay formats (see the examples, pages 46-65). None of these HCV combinations are used as immunogens, but rather as diagnostics. Moreover, each of these combinations includes at least one fusion protein.

Example 65 of Liao describes administration of the core-envelope fusion, without additional HCV regions, to mice. Thus, Liao does not describe immunogenic compositions comprising individual HCV proteins as claimed. Moreover, when used as immunogens, Liao does not include any non-structural regions in the compositions. Although such non-structural regions are used in the diagnostic context, compositions effective for detection of HCV antibodies are not necessarily effective for immunization against HCV. Detection of antibodies merely requires that antibodies specifically bind to an antigenic reagent, whereas eliciting an immune response is complicated by the diverse interactions among the many molecules and cells

of the immune system and their complex regulation, all of which is required to effectively generate cellular and humoral immunity. Thus, problems like antigenic competition and immunodominance (described more fully below), which diminish the efficacy of compositions comprising antigen mixtures in immunization, may not similarly interfere with HCV detection in immunoassays.

Beld relates to immunoassays and the use of the various HCV proteins for detecting HCV. Although Beld describes the variation between genotypes 1 to 3, again this is in the context of diagnostics. Beld fails to test any HCV antigens for efficacy in immunization, nor does Beld suggest combining HCV antigens for immunization purposes.

Valenzuela relates to the use of fusion proteins in immunoassays, not for immunization. The critical elements missing from the combination of Liao, Beld and Valenzuela is the use of individual regions of the HCV polyprotein as claimed in immunogenic compositions.

There can be no reasonable expectation of success that compositions comprising the particular combinations of HCV antigens, as claimed, would be effective in immunization against HCV based on the teachings of these references. The Office has failed to provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007). In fact, the evidence is to the contrary. The cited art fails to provide evidence that a composition comprising individual HCV polypeptides, wherein the HCV polypeptides consist of an NS3, an NS4, an NS5a, NS5b polypeptide and a core polypeptide of HCV, would be particularly effective for immunizing a subject against HCV.

Here, applicants have shown unexpectedly superior results when non-structural HCV polypeptides are provided separately. See, *e.g.*, Example 12 at page 49 of the specification and Figure 2, which show that significantly higher levels of IFN-γ are induced and CD8+ HCV-specific T cells are more effectively activated in response to immunization of mice with a combination of plasmids separately expressing NS34a, NS4ab, and NS5a compared to immunization with a single plasmid expressing the NS345a fusion. The immune response is further enhanced by linking polynucleotides to PLG, particularly when polynucleotides encoding NS3, NS4, and NS5a polypeptides separately are used in immunization (see Figure 2).

A frequent problem with multivalent vaccines is that individual antigen components interfere with one another. An antigen often induces stronger immune responses when it is administered alone than when it is administered in combination with other antigens. It is well known that mixtures of antigens can fail to be effective due to physical interactions among the individual antigens, which result in altered conformation, aggregation or precipitation. Immunological dominance or competition between component antigens can also diminish the response to specific antigens.

Thus, the FDA requires that the efficacy of immunogenic compositions comprising mixtures of antigens be shown even if the efficacy of the individual components has already been demonstrated because of the unpredictability of obtaining effective immunity with mixtures based on the results with individual components. As readily seen, the efficacy of mixed antigen vaccines cannot be predicted.

None of the cited references describe or suggest a composition comprising HCV polypeptides as claimed. Thus, none of the cited references teach or suggest the compositions of the invention. Additionally, there can be no reasonable expectation of success that compositions comprising the particular combinations of HCV antigens would be effective in immunization against HCV based on the teachings of these references.

For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Nonstatutory Double Patenting

The Examiner has provisionally rejected claims 3-5, 8, 45 and 46 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3, 4, 10, 13, 20, 21, 22 and 23 of copending U.S. Patent Application Serial No. 10,281,341. In particular, the Office Action alleges the use of the term "comprising" to describe the claimed composition dies not exclude other elements such as the E1/E2 polypeptide recited in the claims of the '884 application. Office Action, pages 5-6, bridging paragraph.

Applicants request that the rejection be held in abeyance until there is an indication of allowable subject matter in either application. Applicants will then consider the propriety of filing a Terminal Disclaimer.

CONCLUSION

In light of the above remarks, applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Please direct all further written communications regarding this application to:

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Respectfully submitted,

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